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A1

**WO 02/060440**

(54) Title: NOVEL FORMS OF 2,3-DIMETHYL-8-(2-ETHYL-6-METHYLBENZYLAMINO)-IMIDAZO (1,2-A)PYRIDINE-6-CARBOXAMIDE

(57) Abstract: The present invention relates to novel crystalline forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide. Further, the present invention also relates to use of said compounds for the treatment of gastrointestinal disorders, pharmaceutical compositions containing them and processes for obtaining them.

Novel forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo  
(1,2-a)pyridine-6-carboxamide

*Field of the invention*

- 5 The present invention relates to novel crystalline forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide. Further, the present invention also relates to use of said compounds for the treatment of gastrointestinal disorders, pharmaceutical compositions containing them and processes for obtaining them.

10 *Background of the invention and prior art*

In the formulation of drug compositions, it is important for the active pharmaceutical ingredient (API) to be in a form in which it can be conveniently handled and processed. This is of importance, not only from the point of view of obtaining a commercially viable manufacturing process, but also from the point of view of subsequent manufacture of pharmaceutical formulations (e.g. oral dosage forms such as tablets) comprising the active pharmaceutical ingredient.

Further, in the manufacture of oral drug compositions, it is important that a reliable, reproducible and constant plasma concentration profile of the active pharmaceutical ingredient is provided following administration to a patient.

Chemical stability, solid state stability, and "shelf life" of the active pharmaceutical ingredient are also very important factors. The active pharmaceutical ingredient, and compositions containing it, should be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the physico-chemical characteristics of the active pharmaceutical ingredient, e.g. its chemical composition, density, hygroscopicity and solubility.

Amorphous materials may present problems in this regard. For example, such materials are typically more difficult to handle and to formulate, provide for unreliable dissolution, and are often found to be more unstable.

- 5 Thus, in the manufacture of commercially viable and pharmaceutically acceptable drug compositions, it is important, wherever possible, to provide the active pharmaceutical ingredient in a substantially crystalline and stable form.

10 International patent applications WO 99/55705 and WO 99/55706 disclose a number of compounds, referred to as imidazo pyridine derivatives, which are reversible acid pump inhibitors.

15 WO 99/55706 also contains a specific disclosure of the compound 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide. A process for the synthesis of this compound is described in Example 1.4 of WO 99/55706, where the compound is crystallized from ethyl acetate. This process has been shown later to give 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form A.

20 WO 99/55706 contains no information about the solid state properties of the prepared 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide. WO 99/55706 does further not disclose how different crystal forms may be obtained and does not predict the properties of such crystal forms.

*Brief description of the drawings*

25

Figure 1 is an X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form A.

30 Figure 2 is an X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form B.

Figure 3 is an X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form C.

5 Figure 4 is an X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form D.

Figure 5 is an X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form E.

10 Figure 6 is an X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form F.

Figure 7 is an X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form G.

15

*Description of the invention*

It has surprisingly been found that 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide can exist in more than one crystal form. The  
20 compounds are hereinafter referred to as 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide forms A-G. The notation A-G relates to the order in time in which the forms were created, not to their relative thermodynamic stability.

It is thus an object of the present invention to provide crystalline forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide with advantageous  
25 properties.

It is an aspect of the present invention to provide 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form A.

30

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form A, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 1, exhibiting substantially the following d-values and intensities;

Form A		Form A		Form A	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
17.9	vs	5.5	vs	3.87	s
11.6	vs	5.4	m	3.81	m
10.6	m	5.2	m	3.76	m
10.2	vs	5.1	m	3.72	vs
9.0	vs	4.88	m	3.64	s
7.9	m	4.72	s	3.52	m
7.4	m	4.58	m	3.48	w
7.3	w	4.48	m	3.43	m
6.8	m	4.37	m	3.32	s
6.7	s	4.24	m	3.25	w
6.5	w	4.15	m	3.18	m
6.0	m	4.08	m	3.06	w
5.8	m	4.02	vs	2.83	m
5.7	m	3.94	s	2.71	w

The peaks, identified with d-values calculated from the Bragg formula and intensities, have been extracted from the diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form A. The relative intensities are less reliable and instead of numerical values the following definitions are used;

% Relative Intensity*	Definition
25-100	vs (very strong)
10-25	s (strong)

3-10                   m (medium)

1-3                   w (weak)

\* The relative intensities are derived from diffractograms measured with variable slits.

The definition above has also been used when identifying the peaks of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide forms B to G, *vide infra*.

Differential scanning calorimetry (DSC) on form A showed endotherms with extrapolated onset temperatures of *ca* 143°C (*ca* 20 J/g), *ca* 163°C (*ca* 10 J/g), and *ca* 200°C (*ca* 89 J/g).

TGA showed a decrease in mass of *ca* 4.7% (w/w) around 145°C, and a decomposition starting around 250°C.

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form A is a crystalline form exhibiting advantageous properties, such as convenient handling as well as chemical and solid-state stability.

It is a further aspect of the present invention to provide 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form B.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form B, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 2, exhibiting substantially the following d-values and intensities;

Form B		Form B		Form B	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
13.0	w	5.9	s	3.97	m
11.7	m	5.7	m	3.90	m
10.5	vs	5.5	s	3.83	m
9.3	s	5.3	s	3.74	s
7.9	s	5.25	s	3.69	s
7.5	vs	5.18	vs	3.51	m
7.2	m	4.49	m	3.45	s
7.0	m	4.46	m	3.30	s
6.6	m	4.40	s	3.20	m
6.5	m	4.18	m	3.11	m

DSC on form B showed endotherms with extrapolated onset temperatures of *ca* 196°C (*ca* 68 J/g) and *ca* 213°C (*ca* 37 J/g).

5

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form B is a crystalline form exhibiting advantageous properties, such as convenient handling as well as chemical and solid-state stability.

10 It is a further aspect of the present invention to provide 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form C.

15 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form C, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 3, exhibiting substantially the following d-values and intensities;

Form C		Form C		Form C	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
13.2	m	4.55	m	3.32	w
11.8	w	4.44	w	3.27	w
10.8	vs	4.20	w	3.02	w
9.3	w	4.12	w	2.90	w
8.4	s	4.05	w	2.83	w
7.8	vs	3.89	w	2.78	w
7.5	w	3.84	w	2.71	w
6.6	s	3.73	w	2.61	w
5.9	w	3.61	m	2.39	w
5.5	m	3.52	w	2.35	w
5.1	s	3.42	w	2.28	w

DSC on form C showed endotherms with extrapolated onset temperatures of *ca* 201°C (*ca* 5 12 J/g) and *ca* 206°C (*ca* 121 J/g). TGA showed a decomposition starting around 250°C.

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form C is a crystalline form exhibiting advantageous properties, such as convenient handling as well as chemical and solid-state stability.

10

It is a further aspect of the present invention to provide 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form D.

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide 15 form D, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 4, exhibiting substantially the following d-values and intensities;

Form D		Form D	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
33.4	w	5.5	w
17.3	vs	5.2	w
12.3	w	4.64	w
9.9	w	4.34	w
8.7	w	4.15	w
8.1	w	3.88	w
6.5	w	3.76	w
6.0	w	3.23	w
5.8	m	2.90	w

DSC on form D showed endotherms with extrapolated onset temperatures of *ca* 109°C (*ca* 89 J/g), *ca* 159°C (*ca* 19 J/g), *ca* 208°C (*ca* 62 J/g), and *ca* 217°C (*ca* 13 J/g). TGA showed

- 5 a decrease in mass of *ca* 17.9% (w/w) around 115°C, corresponding to a monobutanolate, and a decomposition starting around 250°C.

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide

form D is a crystalline form exhibiting advantageous properties, such as convenient

- 10 handling as well as chemical and solid-state stability.

It is a further aspect of the present invention to provide 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form E.

- 15 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form E, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 5, exhibiting substantially the following d-values and intensities;

Form E		Form E	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
11.7	vs	3.37	m
5.9	m	3.04	s
5.1	vs	3.02	m
4.80	m	2.95	s
4.71	m	2.84	w
4.45	m	2.76	w
4.28	w	2.70	w
4.10	m	2.57	w
3.93	vs	2.53	w
3.88	m	2.51	w
3.72	m	2.36	m
3.40	m	2.12	m

DSC on form E showed an endotherm with extrapolated onset temperature of *ca* 144°C (*ca* 191 J/g). TGA showed a decomposition starting around 165°C.

5

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form E is a crystalline form exhibiting advantageous properties, such as convenient handling as well as chemical and solid-state stability.

- 10 It is a further aspect of the present invention to provide 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form F.

- 15 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form F, according to the present invention, is characterized in providing an X-ray powder diffraction pattern, as in figure 6, exhibiting substantially the following d-values and intensities;

Form F		Form F	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
11.6	w	4.35	w
10.6	vs	4.17	m
9.1	w	3.96	s
7.2	m	3.89	w
6.9	m	3.70	s
6.7	m	3.62	m
5.8	m	3.50	w
5.6	m	3.47	w
5.4	m	3.44	w
5.3	s	3.32	m
4.65	w	3.14	m
4.58	w	2.65	w

DSC on form F showed endotherms with extrapolated onset temperatures of *ca* 154°C (*ca* 92 J/g), *ca* 201°C (*ca* 45 J/g), *ca* 209°C (*ca* 13 J/g), and *ca* 217°C (*ca* 33 J/g). TGA showed

- 5 a decrease in mass of *ca* 11.9% (w/w) around 160°C, probably corresponding to a MEK-solvate, and a decomposition starting around 250°C.

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form F is a crystalline form exhibiting advantageous properties, such as convenient

- 10 handling as well as chemical and solid-state stability.

It is a further aspect of the present invention to provide 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form G.

- 15 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form G, according to the present invention, is characterized in providing an X-ray powder

diffraction pattern, as in figure 7, exhibiting substantially the following d-values and intensities;

Form G		Form G		Form G	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
11.5	14.6	5.2	20.0	3.30	14.5
10.3	100.0	4.64	1.1	3.09	5.6
9.1	2.1	4.58	3.1	3.06	3.3
7.2	7.4	4.43	0.8	2.88	1.4
7.1	1.5	4.35	2.2	2.77	2.1
6.8	3.5	4.17	9.7	2.70	2.1
6.5	5.6	3.98	21.4	2.59	5.3
5.8	2.8	3.87	3.9	2.46	1.7
5.8	12.1	3.63	17.9	2.43	2.0
5.5	10.2	3.56	2.4	2.25	1.1
5.5	10.2	3.45	6.8		
5.3	16.3	3.37	9.9		

- 5 DSC on form G showed endotherms with extrapolated onset temperatures of *ca* 115°C, *ca* 141°C, *ca* 203°C, and *ca* 219°C.

- 2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form G is a crystalline form exhibiting advantageous properties, such as convenient handling as well as chemical and solid-state stability.

- It is possible to crystallize 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide, i.e. the compounds of the present invention in one single solvent or in a mixture of solvents. However, we prefer that the crystallization is from one single solvent.

Crystallization of compounds of the present invention from an appropriate solvent system, containing at least one solvent, may be achieved by attaining supersaturation in a solvent system by solvent evaporation, by temperature decrease, and/or via the addition of anti-solvent (i.e. a solvent in which the compounds of the invention are poorly soluble).

5

Crystallization may also be initiated and/or effected with or without seeding with crystals of the appropriate crystalline compound of the invention.

- Crystallization of compounds of the present invention can be achieved starting from pure  
10 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide of any form, or mixtures of any form.

Compounds of the invention may be prepared in the form of solvates, hydrates, and anhydrides.

15

- Whether an anhydrate or a solvate crystallizes is related to the kinetics and equilibrium conditions of the respective forms at the specific conditions. Thus, as may be appreciated by the skilled person, the crystalline form that is obtained depends upon both the kinetics and the thermodynamics of the crystallization process. Under certain thermodynamic  
20 conditions (e.g. solvent system, temperature, pressure and concentration of compound of the invention), one crystalline form may be more stable than another (or indeed any other). However, crystalline forms that have a relatively low thermodynamic stability may be kinetically favored. Thus, in addition, kinetic factors, such as time, impurity profile, agitation, the presence or absence of seeds, etc. may also influence which form that  
25 crystallizes. Thus, the skilled person, in order to obtain different crystalline forms, may adapt the procedures discussed herein.

- One object of the present invention is to provide processes for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide forms A  
30 to G.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form A can be obtained upon crystallization from ethyl acetate.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide  
5 form B can be obtained upon crystallization from ethyl acetate.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form C can be obtained upon crystallization from methyl ethyl ketone containing methanol.

10 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form D can be obtained upon crystallization from n-butanol.

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form E can be obtained upon crystallization from n-propanol.

15 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form F can be obtained upon crystallization from 2-butanone (methyl ethyl ketone).

20 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form G can be obtained upon crystallization from water.

The preparation and characterization of different forms of compounds of the invention are described hereinafter. Different crystalline forms of the compounds of the invention may be readily characterized using X-ray powder diffraction (XRPD) methods or Raman spectroscopy.

In order to ensure that a particular crystalline form is prepared in the absence of other crystalline forms, crystallization is preferably carried out by seeding with seed crystals of the desired crystalline form. This applies particularly to each of the specific crystalline forms which are described in the Examples.

2,3-Dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide forms A to G obtained according to the present invention are substantially free from other crystal and non-crystal forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide. The term "substantially free from other crystal and non-crystal forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide" shall be understood to mean that the desired crystal form of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide contains less than 50%, preferably less than 10%, more preferably less than 5% of any other forms of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide.

10

In accordance with the invention, the compounds of the invention may be administered and used as described in WO 99/55705 and WO 99/55706, the content of which is hereby incorporated by reference.

15

The compounds of the invention may be further processed before formulation into a suitable pharmaceutical formulation. For example, the crystalline form may be milled or ground into smaller particles.

20

According to a further aspect of the invention, there is provided a pharmaceutical formulation including a compound of the invention in admixture with at least one pharmaceutically acceptable adjuvant, diluent or carrier.

25

According to a further aspect of the invention there is provided a method of treatment of a condition where inhibition of gastric acid secretion is required or desired, which method includes administering a therapeutically effective amount of a compound of the invention to a patient in need of such treatment.

For the avoidance of doubt, by "treatment" we include the therapeutic treatment, as well as the prophylaxis, of a condition.

30

The compounds of the invention have the advantage that they are in a form that provides for improved ease of handling. Further, the compounds of the invention have the advantage that they may be produced in forms that have improved chemical and solid state stability as well as lower hygroscopicity. Thus, the compounds may be stable when stored over prolonged periods.

5 The invention is illustrated, but in no way limited, by the following examples.

*Examples*

10

*General Procedures*

X-ray powder diffraction (XRPD) analysis was performed on samples prepared according to standard methods, for example those described in Giacovazzo, C. et al (1995), Fundamentals of Crystallography, Oxford University Press; Jenkins, R. and Snyder, R. L. (1996), Introduction to X-Ray Powder Diffractometry, John Wiley & Sons, New York; Bunn, C. W. (1948), Chemical Crystallography, Clarendon Press, London; or Klug, H. P. & Alexander, L. E. (1974), X-ray Diffraction Procedures, John Wiley and Sons, New York. X-ray analyses were performed using a Siemens D5000 diffractometer and/or a Philips X'Pert MPD.

15

Differential scanning calorimetry (DSC) was performed using a Mettler DSC820 instrument, according to standard methods, for example those described in Höhne, G. W. H. et al (1996), Differential Scanning Calorimetry, Springer, Berlin.

20

Thermogravimetric analysis (TGA) was performed using a Mettler Toledo TGA850 instrument.

25

DSC onset temperatures may vary in the range  $\pm 5^\circ\text{C}$  (e.g.  $\pm 2^\circ\text{C}$ ), and XRPD distance values may vary in the range  $\pm 2$  on the last decimal place. It should be understood that the d-values of X-ray powder diffraction pattern exhibits variation depending on e.g. equipment used, sample preparation, and operator. However the precision and repeatability

of said technique is found to be high and thus X-ray powder diffraction pattern exhibiting substantially the same d-values should be obtained if repeated.

*Example 1*

- 5 Preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form B

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide (0.72g, 0.0021 mol) was suspended in ethyl acetate and the mixture was heated for a short  
10 while. When the temperature reached R.T. the precipitate was filtered off, washed with ethyl acetate and dried under reduced pressure.

Yield: 0.61g (84%)

*Example 2*

- 15 Preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form C

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide  
20 (44.2g, 0.13 mol) was solved in a refluxing mixture of methyl ethyl ketone (600 ml) and methanol (20 ml). 120 ml of the solvent was evaporated off and the mixture was stirred at 50 °C for 5 h. The mixture was cooled to R.T. and for 72 h. The mixture was cooled with a mixture of ice-water and the product was filtered off. The product was washed with methyl ethyl ketone (100 ml) and was dried at R.T.  
25 Yield: 34.4g, (78 %)

*Example 3*

- Preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form D

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide was suspended in n-butanol and stirred at room temperature for 5 hours whereupon the product was filtered off.

5   *Example 4*

Preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form E

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide was  
10   suspended in n-propanol and stirred at room temperature for 5 hours whereupon the product was filtered off.

*Example 5*

Preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form F

2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide was suspended in 2-butanone and stirred at room temperature for 5 hours whereupon the product was filtered off.

20

*Example 6*

Preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form G

25   To a mixture of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide mesylate (6.0 g, 0.0139 mol) in water (120 ml) was added triethylamine (3.1 g, 0.031 mol). The reaction mixture was stirred at 80 °C for 45 min and the precipitate was filtered off. The solids were suspended in water (50 ml) and were then filtered off. The solids were once again suspended in water and the suspension was heated at 120 °C and a  
30   small amount of water was distilled off. The suspension was filtered warm and the solids

were washed with water (50 ml). The product was dried under reduced pressure at 50 °C for 1 h.

Yield: 4.2g (90 %)

## CLAIMS

1. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form B, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Form B		Form B		Form B	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
13.0	w	5.9	s	3.97	m
11.7	m	5.7	m	3.90	m
10.5	vs	5.5	s	3.83	m
9.3	s	5.3	s	3.74	s
7.9	s	5.25	s	3.69	s
7.5	vs	5.18	vs	3.51	m
7.2	m	4.49	m	3.45	s
7.0	m	4.46	m	3.30	s
6.6	m	4.40	s	3.20	m
6.5	m	4.18	m	3.11	m

2. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form C, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

5

Form C		Form C		Form C	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
13.2	m	4.55	m	3.32	w
11.8	w	4.44	w	3.27	w
10.8	vs	4.20	w	3.02	w
9.3	w	4.12	w	2.90	w
8.4	s	4.05	w	2.83	w
7.8	vs	3.89	w	2.78	w
7.5	w	3.84	w	2.71	w
6.6	s	3.73	w	2.61	w
5.9	w	3.61	m	2.39	w
5.5	m	3.52	w	2.35	w
5.1	s	3.42	w	2.28	w

3. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form D, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

5

Form D		Form D	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
33.4	w	5.5	w
17.3	vs	5.2	w
12.3	w	4.64	w
9.9	w	4.34	w
8.7	w	4.15	w
8.1	w	3.88	w
6.5	w	3.76	w
6.0	w	3.23	w
5.8	m	2.90	w

4. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form E, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

5

Form E		Form E	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
11.7	vs	3.37	m
5.9	m	3.04	s
5.1	vs	3.02	m
4.80	m	2.95	s
4.71	m	2.84	w
4.45	m	2.76	w
4.28	w	2.70	w
4.10	m	2.57	w
3.93	vs	2.53	w
3.88	m	2.51	w
3.72	m	2.36	m
3.40	m	2.12	m

5. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form F, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

Form F		Form F	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
11.6	w	4.35	w
10.6	vs	4.17	m
9.1	w	3.96	s
7.2	m	3.89	w
6.9	m	3.70	s
6.7	m	3.62	m
5.8	m	3.50	w
5.6	m	3.47	w
5.4	m	3.44	w
5.3	s	3.32	m
4.65	w	3.14	m
4.58	w	2.65	w

6. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form G, characterized in providing an X-ray powder diffraction pattern exhibiting substantially the following d-values:

5

Form G		Form G		Form G	
d-value (Å)	Relative intensity	d-value (Å)	Relative intensity	d-value (Å)	Relative intensity
11.5	14.6	5.2	20.0	3.30	14.5
10.3	100.0	4.64	1.1	3.09	5.6
9.1	2.1	4.58	3.1	3.06	3.3
7.2	7.4	4.43	0.8	2.88	1.4
7.1	1.5	4.35	2.2	2.77	2.1
6.8	3.5	4.17	9.7	2.70	2.1
6.5	5.6	3.98	21.4	2.59	5.3
5.8	2.8	3.87	3.9	2.46	1.7
5.8	12.1	3.63	17.9	2.43	2.0
5.5	10.2	3.56	2.4	2.25	1.1
5.5	10.2	3.45	6.8		
5.3	16.3	3.37	9.9		

7. A process for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form B as defined in claim 1 comprising the steps of:
- 10 a) dissolving or suspending 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide of any form, or a mixture of any form in ethyl acetate,
- b) allowing the solution or suspension to crystallize, and
- c) isolating the 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form B thus obtained.
- 15

8. A process for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form C as defined in claim 2 comprising the steps of:
  - a) dissolving or suspending 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide of any form, or a mixture of any form in methyl ethyl ketone containing methanol,
  - b) allowing the solution or suspension to crystallize, and
  - c) isolating the 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form C thus obtained.
- 10 9. A process for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form D as defined in claim 3 comprising the steps of:
  - a) dissolving or suspending 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide of any form, or a mixture of any form in n-butanol,
  - b) allowing the solution or suspension to crystallize, and
  - c) isolating the 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form D thus obtained.
- 15 10. A process for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form E as defined in claim 4 comprising the steps of:
  - a) dissolving or suspending 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide of any form, or a mixture of any form in n-propanol,
  - b) allowing the solution or suspension to crystallize, and
  - c) isolating the 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form E thus obtained.
- 20
- 25
- 30

11. A process for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form F as defined in claim 5 comprising the steps of:
  - a) dissolving or suspending 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide of any form, or a mixture of any form in methyl ethyl ketone,
  - b) allowing the solution or suspension to crystallize, and
  - c) isolating the 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form F thus obtained.
- 10 12. A process for the preparation of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form G as defined in claim 6 comprising the steps of:
  - a) dissolving or suspending 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide of any form, or a mixture of any form in water,
  - b) allowing the solution or suspension to crystallize, and
  - c) isolating the 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form G thus obtained.
- 20 13. A process according to any of claims 7-12, characterized in that seeds are added to the solution/suspension to induce crystallization.
14. 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide prepared according to any of claims 7-13.
- 25 15. A pharmaceutical formulation comprising 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide as defined in any of claims 1-6 in admixture with at least one pharmaceutically acceptable excipient.

16. The use of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide as defined in any of claims 1-6 in therapy.
17. The use of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide as defined in claims 1-6 as active ingredient in the manufacture of a medicament for use in treatment of gastrointestinal disorders.
18. A method of treatment of gastrointestinal disorders which comprises administration of a therapeutically effective amount of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide as defined in any of claims 1-6, to a patient suffering from gastrointestinal disorders.

Figure 1. X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form A measured with variable slits.

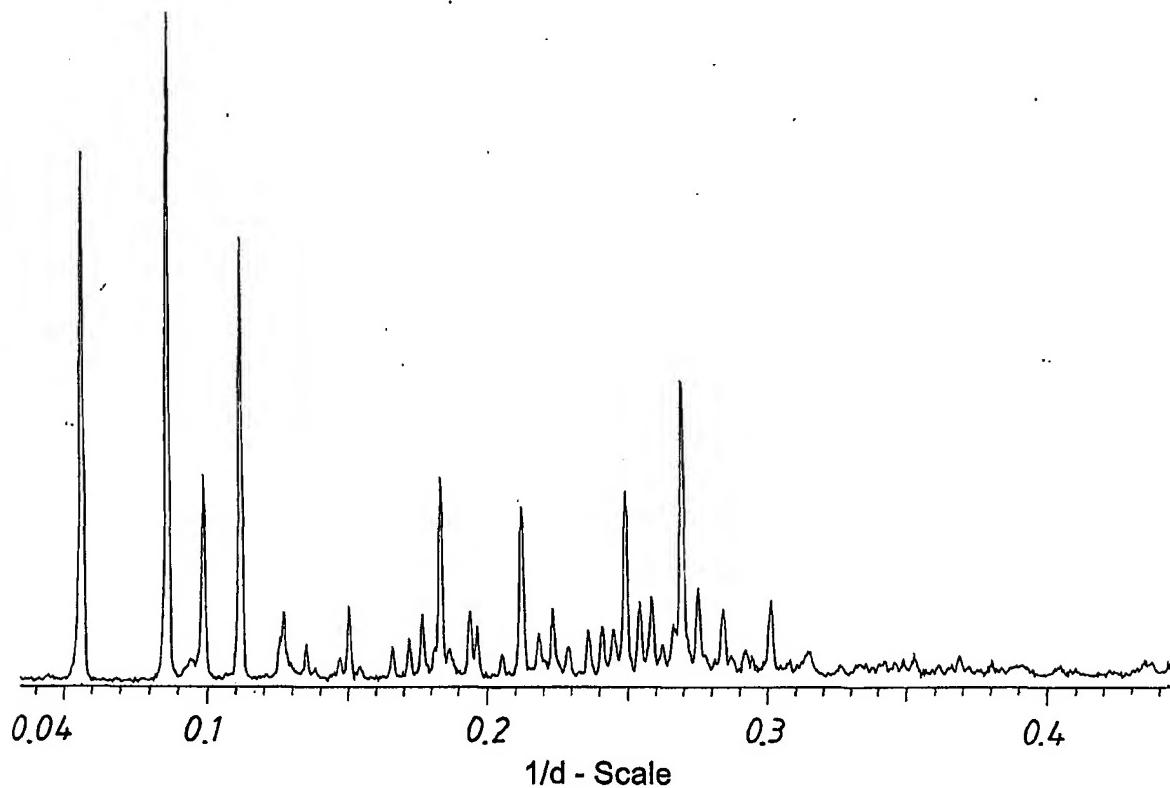


Figure 2. X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form B measured with variable slits.

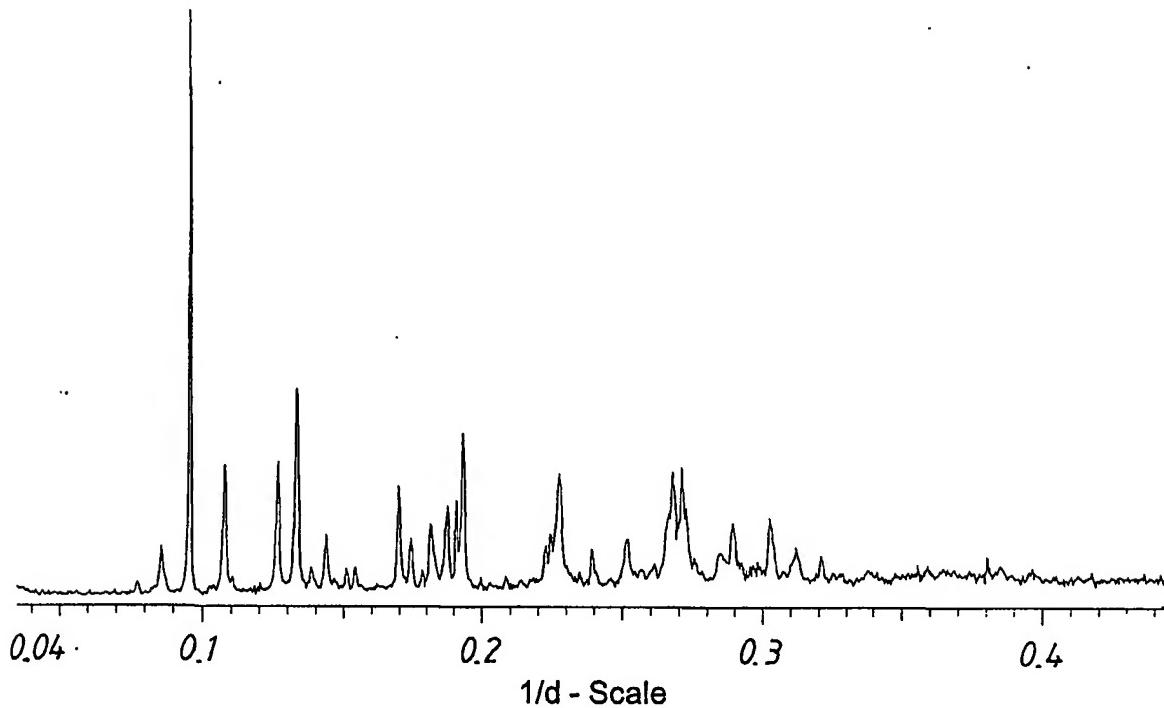


Figure 3. X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form C measured with variable slits.

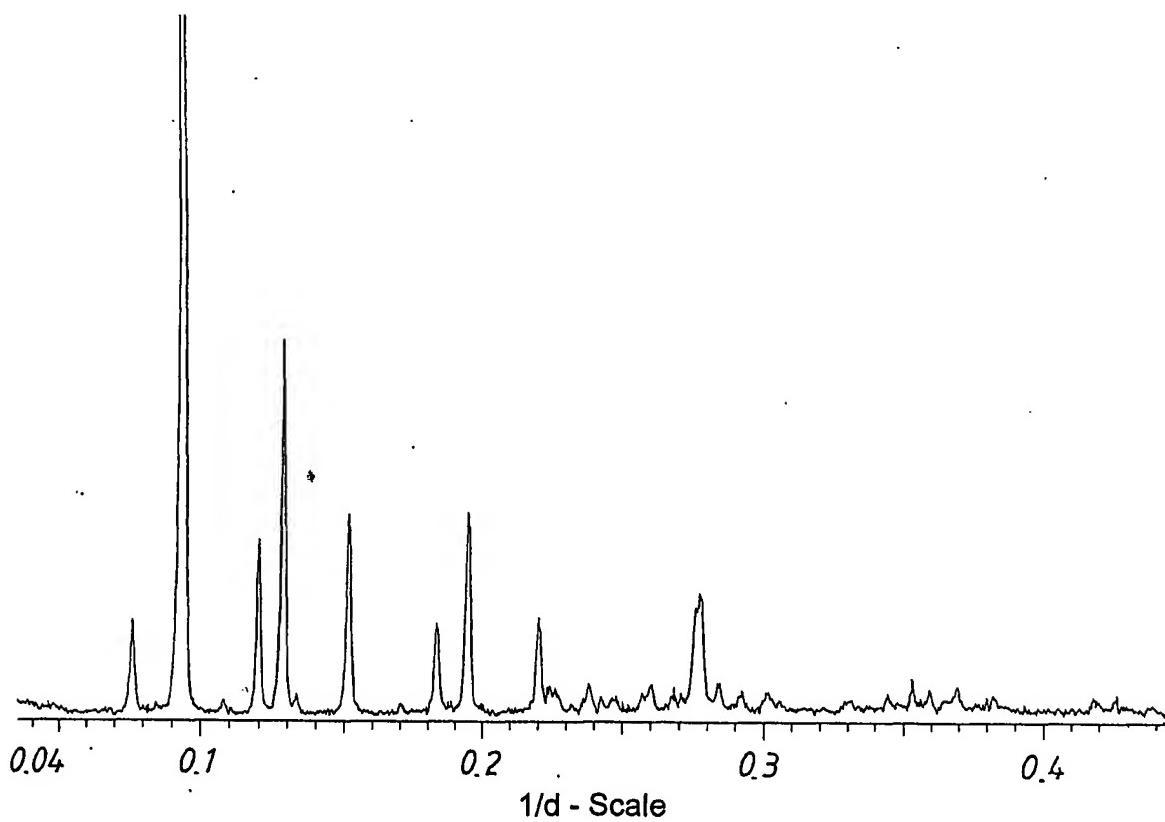


Figure 4. X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form D measured with variable slits.

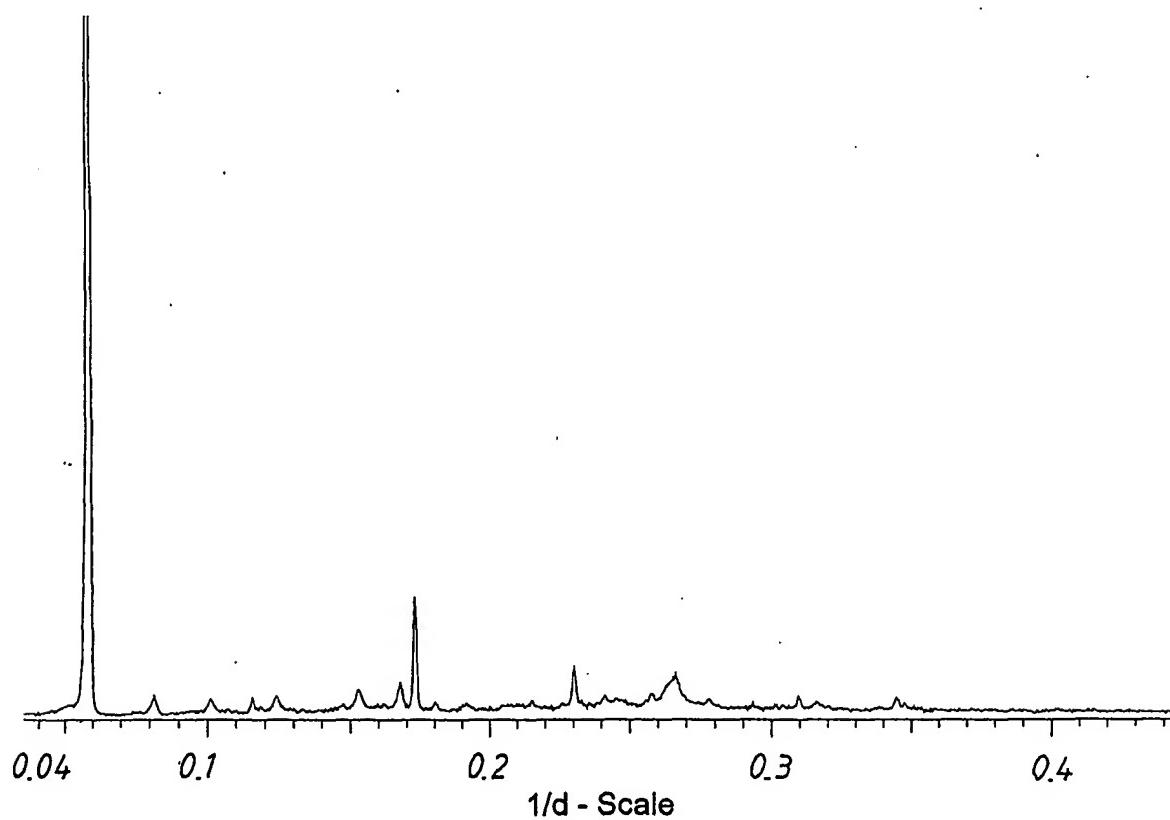
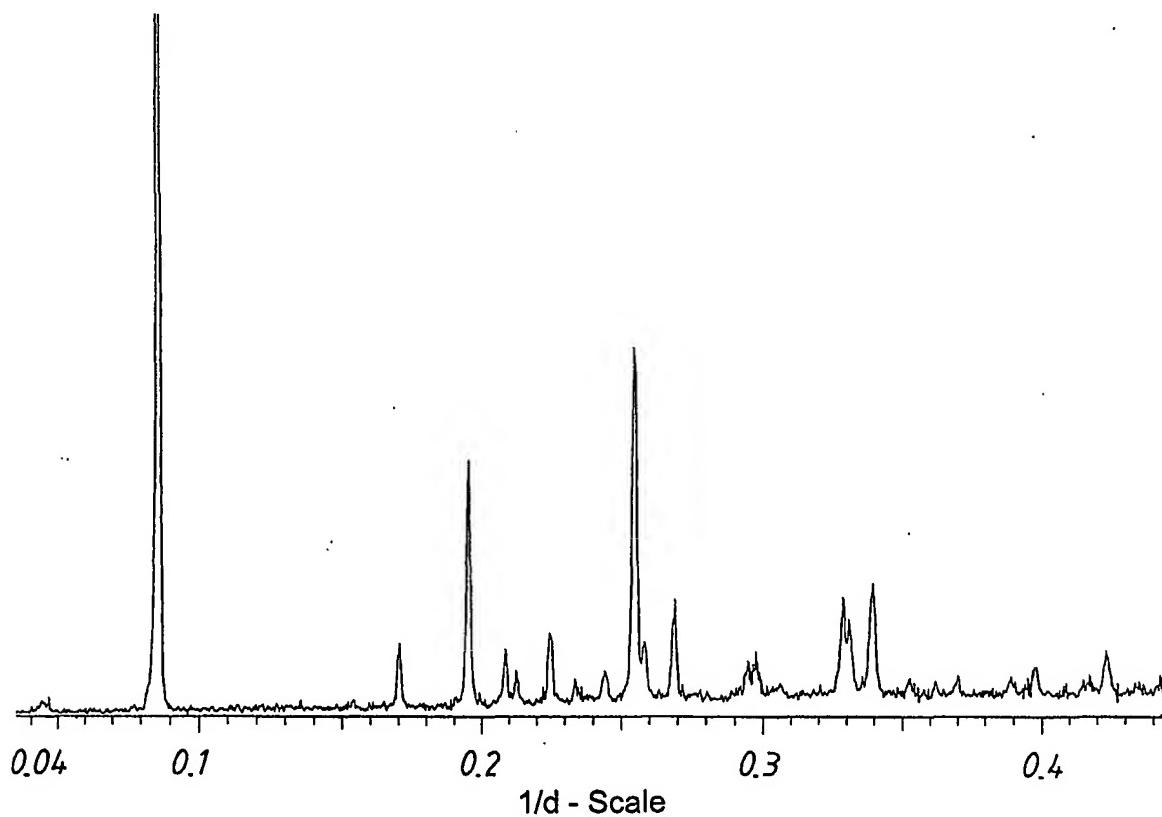
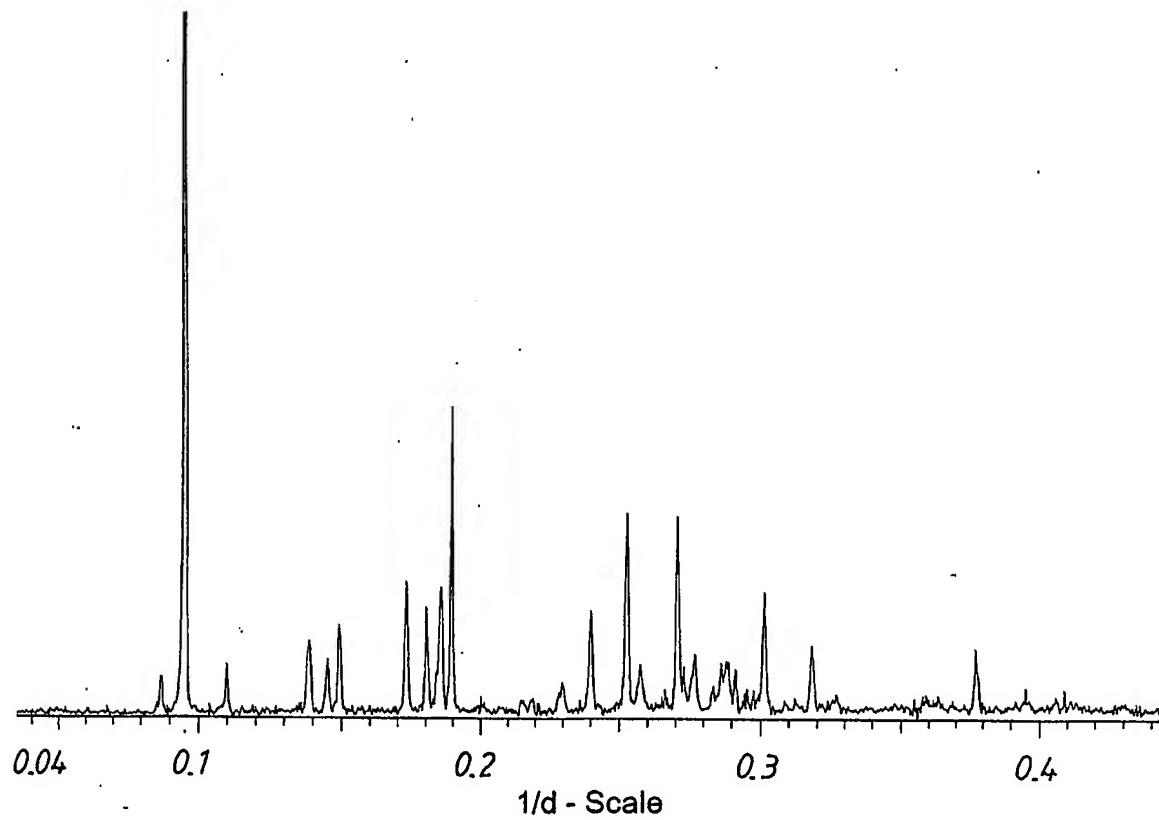


Figure 5. X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form E measured with variable slits.



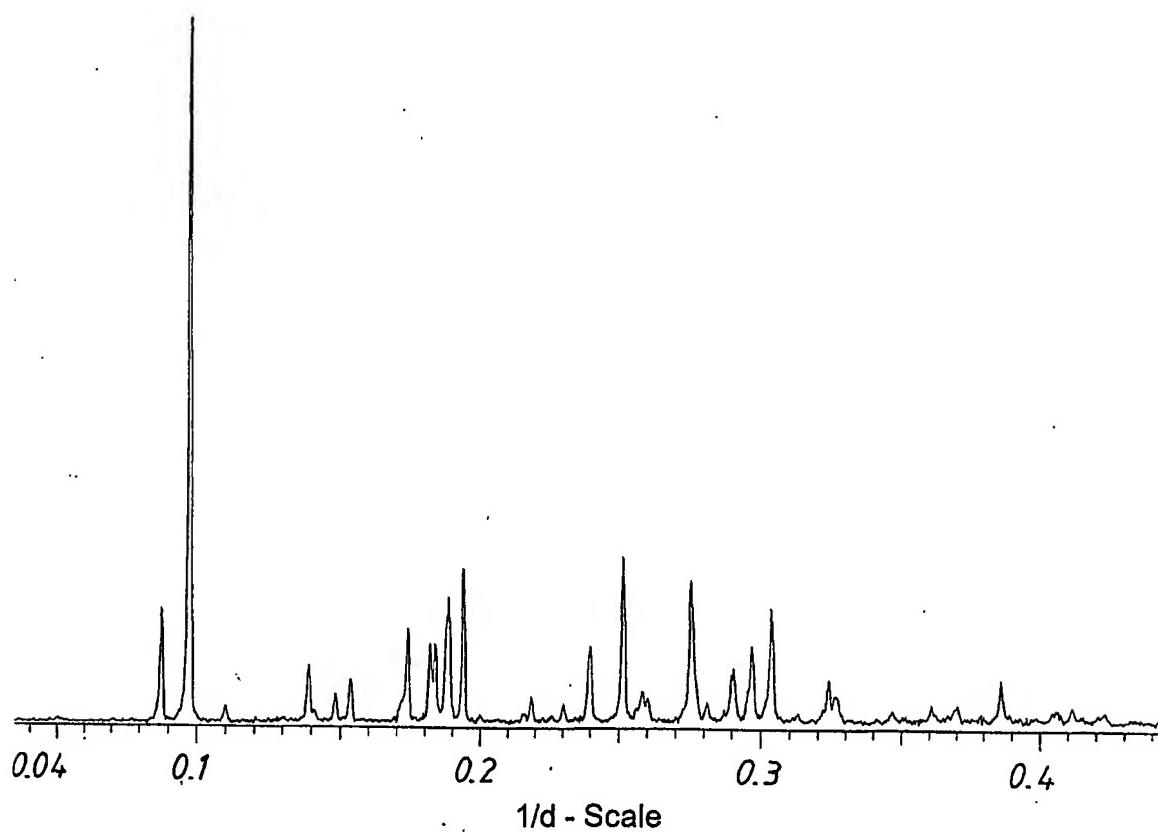
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Figure 6. X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form F measured with variable slits.



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Figure 7. X-ray powder diffractogram of 2,3-dimethyl-8-(2-ethyl-6-methylbenzylamino)-imidazo[1,2-a]pyridine-6-carboxamide form G measured with variable slits.



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 02/00162

## A. CLASSIFICATION OF SUBJECT MATTER

**IPC7: A61K 31/4188, A61K 31/437, C07D 471/04, A61P 1/00**  
 According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

**IPC7: A61K, C07D, A61P**

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

**SE,DK,FI,NO classes as above**

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

**CHEM. ABS DATA, BIOSIS, EMBASE, MEDLINE, EPO-INTERNAL, WPI DATA**

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9955706 A1 (ASTRA AKTIEBOLAG), 4 November 1999 (04.11.99), page 24, example 1.4; abstract; claim  -- -----	1-18

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	
"A"	document defining the general state of the art which is not considered to be of particular relevance
"E"	earlier application or patent but published on or after the international filing date
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O"	document referring to an oral disclosure, use, exhibition or other means
"P"	document published prior to the international filing date but later than the priority date claimed
"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X"	document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y"	document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&"	document member of the same patent family

Date of the actual completion of the international search

13 May 2002

Date of mailing of the international search report

14 -05- 2002

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**INTERNATIONAL SEARCH REPORT**International application No.  
**PCT/SE02/00162****Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: **16, 18**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see next sheet**
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**International application No.  
**PCT/SE02/00162**

Claims 16-18 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

01/05/02

International application No.

PCT/SE 02/00162

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9955706 A1	04/11/99	AU 727349 B	14/12/00
		AU 4300699 A	16/11/99
		AU 4300799 A	16/11/99
		AU 9098998 A	22/03/99
		BR 9909995 A	26/12/00
		BR 9909996 A	26/12/00
		CA 2329921 A	04/11/99
		CA 2329922 A	04/11/99
		CN 1306533 T	01/08/01
		CN 1307577 T	08/08/01
		EE 200000626 A	15/04/02
		EE 200000664 A	15/04/02
		EP 1011653 A	28/06/00
		EP 1073656 A	07/02/01
		EP 1073657 A	07/02/01
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		JP 2001514215 T	11/09/01
		NO 20001087 A	02/03/00
		NO 20005450 A	22/12/00
		NO 20005451 A	27/12/00
		PL 338982 A	04/12/00
		PL 343797 A	10/09/01
		PL 343801 A	10/09/01
		SE 9801526 D	00/00/00
		SK 14912000 A	11/06/01
		SK 14922000 A	11/06/01
		TR 200003149 T	00/00/00
		TR 200003176 T	00/00/00
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		US 6313137 B	06/11/01
		WO 9955705 A	04/11/99